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Regioselective upper rim substitution of calix[4]arenes

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ABSTRACT

The electrophilic substitution of 25,27-dipropoxy-26,28-dinosyloxycalix[4]arene leads exclusively to the *para*-substitution of the alkylated phenol rings, while in the next step, the protecting nosyl group can be easily removed using a basic hydrolysis. The overall process yields dialkoxycalix[4]arenes with the substitution on the alkylated rings—the substitution pattern, which is complementary to the common dialkoxycalix[4]arenes with substituted nonalkylated phenolic units. The usefulness of this protection/deprotection procedure was documented by the synthesis of novel type of calixarene dipropoxy derivatives, and by the preparation of a novel anion receptor based on this substitution pattern.

1. Introduction

Calixarenes,[1] a class of synthetic macrocycles consisting of phenolic units linked together by methylene bridges, are very frequently used in the design of sophisticated receptors and host molecules. Among them, derivatives of calix[4]arene deserve special attention due to their unique three-dimensional structures and/or easy chemical modifications. As the chemistry of calix[4]arene is well established, many regioselective or stereoselective derivatisation methods are currently in use.[1] The existence of four basic conformations-atropoisomers (*cone*, *partial cone*, 1,2-*alternate* and 1,3-*alternate*) makes calix[4]arene derivatives ideal candidates for applications in supramolecular chemistry.[2] Typically, the calix[4]arene moiety, blocked in the specific conformation, serves as a molecular scaffold, which enables the introduction of selected functional groups or structural fragments into precisely defined mutual positions in space. Depending on the substitution, these highly preorganised molecules can then be used as receptors for ions or neutral molecules.[3]

Dialkoxy derivatives of calix[4]arene are easily accessible from the basic calixarene and they are commonly used as the starting point in the derivatisation of calixarenes.[4] The electrophilic substitution of these compounds attacks exclusively the *para*-positions of nonsubstituted phenolic units leading finally to the substitution pattern A (Fig. 1).[5] During our experiments with regioselective derivatisation of the calixarene skeleton we found that dipropoxy dibenzoyloxy derivatives are nitrated only on alkylated rings while the phenolic units bearing benzoyl ester groups remained untouched by the substitution. This rather unexpected result attracted our attention to the use of ester functions as protecting groups in the aromatic electrophilic substitution reaction. In this paper we report the advantageous application of nosyl groups in the lower-rim protection/deprotection strategy allowing the preparation of derivatives possessing so far almost unknown[6] substitution pattern B in high yields.

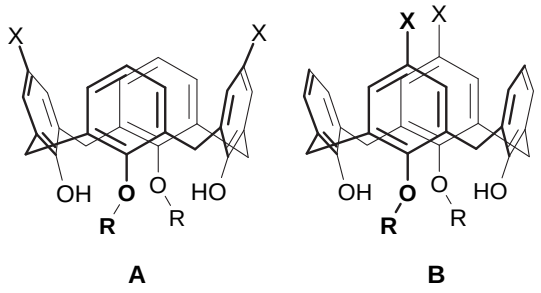

Fig. 1. Two different substitution patterns in dialkylated calix[4]arenes.

2. Results and discussion

The alkylation of basic calix[4]arene (PrI/K_2CO_3/acetone) gave a distally dialkylated compound **1**,[7] which was used as the starting point for subsequent regioselective transformations. Our initial attempts at the acylation of free OH groups were carried out with benzoyl chloride. Unfortunately, these reactions did not give good

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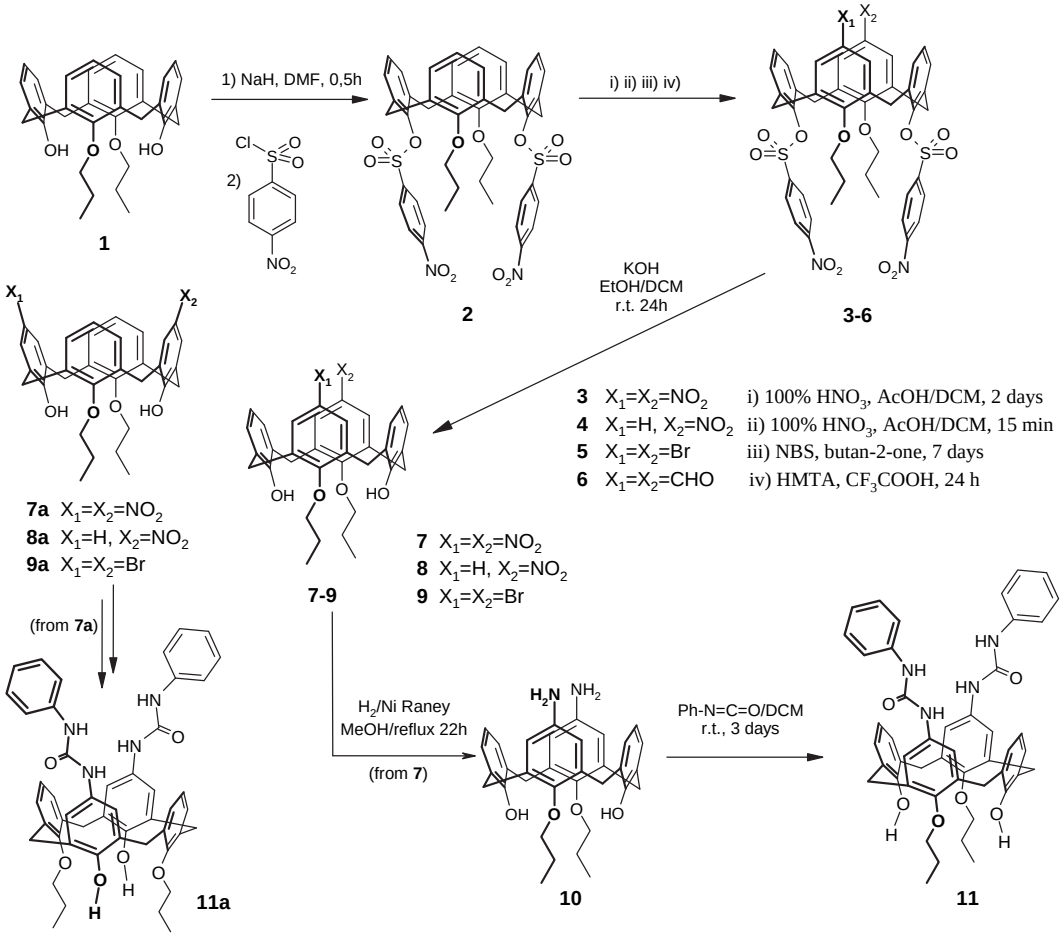
yields of diacylated compounds. Moreover, the product was usually obtained as an inseparable mixture of two conformations (*cone* and *partial cone*) that hindered analysis and subsequent applications of these compounds. During our preliminary study we found that *p*-nitrobenzene sulfonyl chloride (nosyl chloride) is a suitable agent for lower rim acylation as it smoothly led to ester **2** in a 90% yield.

The regioselectivity of the electrophilic substitution of **2** was studied using nitration[8] as a model reaction. It was carried out using 100% HNO_3 in a AcOH/DCM mixture at room temperature. Depending on the reaction conditions (reaction time, excess of a nitric acid) both mono- and dinitro derivatives **4** and **3** can be obtained in 62% and 85% yields, respectively. In all cases, contrary to our expectations, only one regioisomer was isolated from the reaction mixture (Scheme 1). The ^{1}H NMR spectrum of **3** clearly proves the formation of distally *p*-disubstituted product. Thus, derivative **3** possesses one singlet of nitrosubstituted phenyl rings (δ 8.22 ppm), a doublet and triplet due to the unsubstituted rings (δ 6.33 and 6.55 ppm) with typical interaction constant ($J \approx 7.8$ Hz) in the aromatic part of spectrum. At the same time, characteristic doublets of bridging $-CH_2-$ units (3.89 and 3.28 ppm, $J \approx 13$ Hz) exactly correspond to the *cone* conformation of the calixarene skeleton .

signals. Unfortunately, we have not succeeded with growing of suitable monocrystals for X-ray crystallography. To clarify the place of attack we have carried out the next step—deprotection of calixarene lower rim. Stirring of **3** with KOH in a EtOH/DCM mixture and subsequent acidification with aqueous HCl gave dinitro dipropoxy compound in a 92% yield. The comparison with the original sample of **7a** (formed by direct nitration[5a] of dipropoxy calixarene **1**) revealed that the structure of our compound corresponds to formula **7** with nitro groups on alkylated phenol moieties (substitution pattern B, Fig. 1). Interestingly, while the splitting pattern and multiplicity of signals in ^{1}H NMR spectra of **7** and **7a** are identical, the corresponding chemical shifts are very distinct. Thus, the signal of OH group in derivative **7** appears at 7.96 ppm, while the same group in compound **7a** is shifted to 9.44 ppm because of the electron-withdrawing effect of the $-NO_2$ substituent.

Hence, a simple synthetic strategy consisting of (i) protection of the lower rim with nosyl group, (ii) electrophilic substitution of the upper rim and (iii) final deprotection of nosylate, gives us an opportunity to synthesise dialkoxycalixarenes with complementary substitution pattern to those isomers formed by direct electrophilic substitution of dialkylated compounds (compare **7** vs **7a**). Interestingly, under no conditions (higher temperature, long reaction



Scheme 1. Preparation of 5,17-disubstituted-26,28-dipropoxycalix[4]arene-25,27-diols **7**–**9** and anion receptor **11**.

On the other hand, the ^{1}H NMR spectra did not allow the unequivocal assignment of the correct position of the nitro groups as theoretically two regioisomers are possible: (i) *para*-position of alkoxysubstituted rings, or (ii) *para*-position of aromatic moieties bearing sulfonates. It is evident that both regioisomers should possess the same multiplicity and the identical splitting pattern of

time, high excess of 100% nitric acid) we were able to isolate higher nitrated products (tri- or tetra-nitrated). This demonstrates a very strong deactivating effect of nosyl groups if compared with alkoxy derivatives, which is reflected in the strict regioselectivity of dinosylated intermediate (compound **2**) in electrophilic substitution.

To show the general applicability of this synthetic procedure we have carried out several other electrophilic substitution reactions (Scheme 1). Thus, compound **2** was regioselectively brominated using NBS in butan-2-one to form derivative **5** in an 88% yield. Interestingly, the same reaction carried out in $CHCl_3$ did not give any product and only the starting compound was isolated. Duff formylation[9] (urotropine/TFA, reflux) of **2** led similarly to the diformyl derivative **6** in 75% yield. The dibromo derivative was then deprotected by basic hydrolysis of nosyl groups (KOH/EtOH) to give dibromodiol **9** in 97% yield (optimised). Unfortunately, similar deprotection of diformyl derivative **6** was not possible due to the presence of formyl groups, which are noncompatible with the reaction conditions. Hence, this compound could only be deprotected after the transformation of formyl groups into more stable functional moieties.

An interesting phenomenon was encountered if we compared the solubility of the corresponding regioisomers. Dibromo derivative **9a**[10] is only very scarcely soluble in common organic solvents. On the other hand, isomer **9** is perfectly soluble in DCM or chloroform. A similar trend was observed for the comparison of nitroderivatives **7** versus **7a**. As shown by IR spectroscopy (KBr disc) the OH vibrations in **7a** can be found at 3198 cm^{-1} while compound **7** shows the peak at 3366 cm^{-1}. The difference in OH wavelength indicates a different strength of the corresponding hydrogen bonds on the lower rim.

To show the usefulness of these novel regioisomers in calix[4]arene chemistry we decided to transform nitro derivative **7** into the corresponding anion receptor **11** and to compare its complexation ability with a recently reported[11] receptor **11a** possessing the inverse substitution pattern. Thus, derivative **7** was reduced using Raney nickel[12] in methanol under reflux conditions to yield amino substituted compound **10** in 73% yield. Interestingly, our attempts to use $SnCl_2$ as a common reducing agent in calixarene chemistry failed due to the problems with the isolation of products (the presence of free OH groups leads probably to the formation of tin complexes). Amino calixarene **10** was then reacted with phenyl isocyanate in DCM at room temperature to give smoothly the target receptor **11** in 79% yield.

The complexation capacity of ligand **11** was studied by standard ^{1}H NMR titration experiments using a constant calixarene concentration and an increasing concentration of appropriate anion to obtain different host/guest ratios (1–20:1). To ensure the solubility of both organic (ligand) and inorganic (anions) constituents, a mixed solvent system ($CDCl_3$/DMSO-d_6=4:1, v/v) was used. All anions were added as their tetrabutylammonium salts to avoid potential interactions of calixarene cavity with counter cations. The addition of anions led to the down-field shifts of ureido NH– (1.5 ppm) and neighbouring aromatic signals in the ^{1}H NMR spectra indicating the complexation phenomenon under fast exchange conditions. As the signals of –NH– protons became remarkably broadened upon addition of anions, the corresponding binding constants were calculated from the complexation induced shifts (CIS) of neighbour aromatic CH protons (*meta*-positions). These shifts were usually around 60–70 Hz upon the addition of 5 equiv of anions. Fig. 2a shows a typical binding isotherm corresponding to the formation of a 1:1 complex. The stoichiometry of the complexes was also verified by the independent Job plot measuring (Fig. 2b). The results obtained are summarised in Table 1 where previously described compound **11a** has been taken as model compound for the comparison. It is obvious that compound **11** shows very similar complexation ability towards spherical anions (halides) when compared with model **11a**. On the other hand, receptor **11** shows remarkable selectivity for tetrahedral dihydrogen phosphonate anion K=1400±200 l mol^{-1}, and also carboxylates (acetate, benzoate) are bound somewhat more strongly by this compound. The results indicate that novel type of calix[4]arene substitution pattern

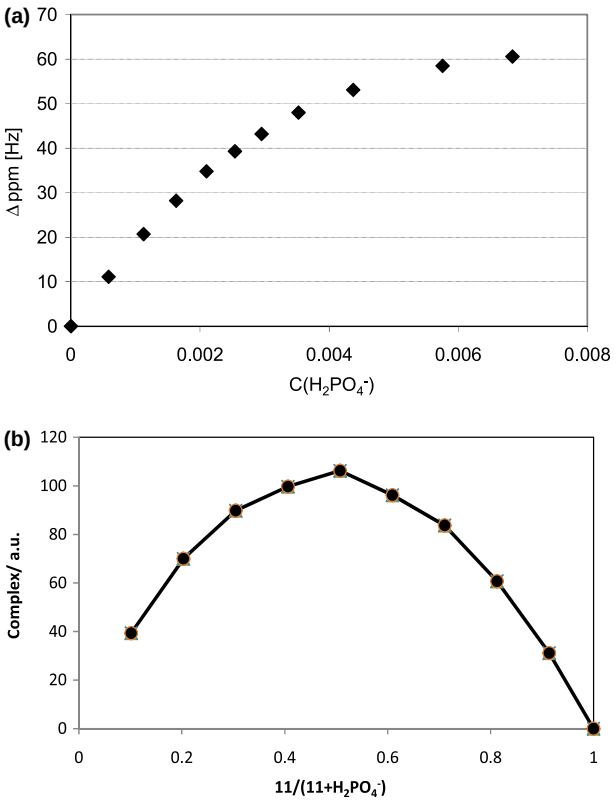


Fig. 2. (a) Binding isotherm of ligand **11** with $H_2PO_4^-$ anion; (b) Job plot for the same system in $CDCl_3$/DMSO-d_6 4:1, v/v system (^{1}H NMR titration, 300 MHz, 298 K).

Table 1
Binding constants K [M^{-1}] of receptor **11** and **11a** with selected anions (^{1}H NMR titration, $CDCl_3$/DMSO-d_6 4:1, v/v system, 300 MHz, 298 K)

Anion[a]	K [M^{-1}]	
	11a[b]	**11**
Cl^-	60 ± 10	44 ± 4
Br^-	20 ± 10	31 ± 6
I^-	[c]	20 ± 6
$H_2PO_4^-$	420 ± 20	1400 ± 200
CH_3COO^-	250 ± 20	370 ± 70
$PhCOO^-$	130 ± 10	185 ± 35

[a] Anions were added as tetrabutylammonium salts.
[b] From Ref. 11.
[c] Too small changes in chemical shifts upon addition of anion.

can lead to interesting applications in supramolecular chemistry and can serve as a complementary/inverse pattern in the design of calixarene-based receptors.

3. Conclusions

In conclusion, we have demonstrated the usefulness of nosyl groups in the selective derivatisation of the upper rim of calixarenes. The introduction of nosyl groups into the lower rim of dialkylated calix[4]arenes enables the regioselective substitution of alkoxyphenol moieties. The final deprotection of these compounds leads to the so far unavailable regioisomers, which possess a different substitution pattern when compared with the same compounds available by direct electrophilic substitution. The application of novel regioisomers in the design of calixarene-based receptors was demonstrated by the synthesis of novel anion receptor based on this substitution pattern.

4. Experimental

4.1. General

Melting points were determined on a Boetius block (Carl Zeiss Jena, Germany) and are not corrected. The IR spectra were measured on an FT-IR spectrometer Nicolet 740 in $CHCl_3$ and/or in KBr. ^1H NMR spectra were recorded on a Varian Gemini 300 spectrometer. Dichloromethane used for the reaction was dried with CaH_2 and stored over molecular sieves. The purity of the substances and the courses of reactions were monitored by TLC using TLC aluminium sheets with Silica gel 60 F_{254} (Merck). Preparative TLC chromatography was carried out on 20×20 cm glass plates covered by Silica gel 60 GF_{254} (Merck).

Starting compound **1**[7] was prepared according to known procedure. The corresponding regioisomers **7a**,[12] **8a**,[5b] **9a**[10] and **11a**[11] were described in the literature.

4.2. Synthesis of 25,27-bis(*p*-nitrobenzenesulfonyloxy)-26,28-dipropoxycalix[4]arene (*cone*) 2

A mixture of 26,28-dipropoxycalix[4]arene-25,27-diol **1** (5.00 g, 9.83 mmol) and sodium hydride (1.60 g, 39.30 mmol, 60% suspension in mineral oil) was stirred for 30 min at 0 °C in anhydrous DMF (200 ml). Then, *p*-nitrobenzene sulfonyl chloride (8.71 g, 39.30 mmol) was added and the reaction mixture was stirred at room temperature for 7 days. The resulting mixture was acidified with 1 M hydrochloric acid and extracted with CH_2Cl_2 (3×100 ml). The combined organic layers were washed with water (300 ml), brine (300 ml) and dried over $MgSO_4$. Organic solvent was removed under reduced pressure, and the oily residue was dissolved in CH_2Cl_2 (10 ml) and precipitated by addition of methanol (150 ml). The precipitate was filtered off, washed twice with methanol and dried to give 7.76 g (90%) of product **2** as a yellowish powder, mp: 250–254 °C. ^1H NMR (300 MHz; $CDCl_3$, TMS): δ_H 8.41–8.38 (4H, m, Ar–H (Nos)), 8.05–8.02 (4H, m, Ar–H (Nos)), 7.05 (4H, d, *J*=7.3 Hz, Ar–H), 6.91 (2H, t, *J*=7.5 Hz, Ar–H), 6.40 (2H, t, *J*=7.8 Hz, Ar–H), 6.19 (4H, d, *J*=7.6 Hz, Ar–H), 3.98 (4H, d, *J*=13.8 Hz, Ar–CH_2–Ar *ax*), 3.81 (4H, t, *J*=8.4 Hz, 2× OCH_2), 2.83 (4H, d, *J*=13.8 Hz, Ar–CH_2–Ar *eq*), 1.93–1.79 (4H, m, 2× OCH_2CH_2), 0.87 (6H, t, *J*=7.5 Hz, 2× CH_3). ^{13}C NMR (75 MHz; CD_2Cl_2): δ 157.4, 151.3, 144.3, 141.8, 135.9, 134.4, 130.2, 129.6, 128.6, 125.8, 124.7, 123.0, 76.8, 31.9, 23.3, 9.9. TOF MS (ES^+) *m*/*z* (%): for $C_{46}H_{42}N_2O_{12}S_2$ (878.98) found: 901.6 (100) $[M+Na]^+$. EA calcd for $C_{46}H_{42}N_2O_{12}S_2$, C, 62.86; H, 4.47; N, 3.19; S, 6.94%. Found C, 62.66; H, 4.32; N, 3.11; S, 6.85%.

4.3. Synthesis of 5,17-dinitro-25,27-bis(*p*-nitrobenzenesulfonyloxy)-26,28-dipropoxycalix[4]arene (*cone*) 3

Nitric acid (4 ml, 100%) was added dropwise to a solution of calix[4]arene **2** (1.00 g, 1.14 mmol) in dry dichloromethane (100 ml) and glacial acetic acid (12 ml). The reaction mixture was stirred for 48 h at room temperature, poured into water and extracted with CH_2Cl_2 (3×100 ml). The combined organic layers were washed with water (200 ml), then with saturated aqueous $NaHCO_3$ (200 ml) and dried over $MgSO_4$. The solvent was removed under reduced pressure to give 936 mg (85%) of product **3** as an orange powder, mp: 260 °C (decomp.). ^1H NMR (300 MHz; $(CD_3)_2SO$): δ_H 8.52–8.48 (4H, m, Ar–H (Nos)), 8.22 (4H, s, Ar–H), 8.13–8.10 (4H, m, Ar–H (Nos)), 6.55 (2H, t, *J*=7.8 Hz, Ar–H), 6.33 (4H, d, *J*=7.9 Hz, Ar–H), 3.89 (4H, d, *J*=13.2 Hz, Ar–CH_2–Ar *ax*), 3.81 (4H, t, *J*=8.1 Hz, 2× OCH_2), 3.28 (4H, d, *J*=13.5 Hz, Ar–CH_2–Ar *eq*), 1.75–1.66 (4H, m, 2× OCH_2CH_2), 0.74 (6H, t, *J*=7.5 Hz, 2× CH_3). ^{13}C NMR (75 MHz; $(CD_3)_2SO$): δ 163.3, 151.9, 143.8, 143.0, 140.2, 137.4, 133.7, 130.7, 129.4, 126.8, 126.0, 125.5, 77.3, 31.1, 23.4, 10.0. TOF MS (ES^+) *m*/*z* (%): for $C_{46}H_{40}N_4O_{16}S_2$ (968.98) found: 991.3 (100) $[M+Na]^+$. EA calcd for $C_{46}H_{40}N_4O_{16}S_2$, C, 57.02; H, 4.16; N, 5.78; S, 6.62%. Found C, 56.90; H, 4.11; N, 5.71; S, 6.59%.

4.4. Synthesis of 5-mononitro-25,27-bis(*p*-nitrobenzenesulfonyloxy)-26,28-dipropoxycalix[4]arene (*cone*) 4

A mixture of calix[4]arene **2** (1.50 g, 1.71 mmol) in dry dichloromethane (17.1 ml) and glacial acetic acid (17.1 ml) was cooled to 0 °C in an ice bath and 5.7 ml of 100% nitric acid was added. The mixture was stirred for 15 min, poured into water and extracted with CH_2Cl_2 (3×100 ml). The combined organic layers were washed with water (200 ml), then with saturated $NaHCO_3$ (200 ml) and dried over $MgSO_4$. The solvent was removed under reduced pressure. Crude product was purified by column chromatography on silica gel (CH_2Cl_2/hexane=17:1, v:v) to yield 980 mg (62%) of title compound as a yellow powder, mp: 270 °C (decomp.). ^1H NMR (300 MHz; $CDCl_3$, Me_4Si): δ_H 8.43–8.40 (4H, m, Ar–H (Nos)), 8.04–8.00 (6H, m, Ar–H+Ar–H (Nos)), 7.02 (2H, d, *J*=7.6 Hz, Ar–H), 6.90 (1H, t, *J*=6.5 Hz, Ar–H), 6.46 (2H, t, *J*=7.8 Hz, Ar–H), 6.25–6.21 (4H, m, Ar–H), 4.13 (2H, d, *J*=14.1 Hz, Ar–CH_2–Ar *ax*), 4.01 (2H, t, *J*=8.2 Hz, 1× OCH_2), 3.87 (2H, d, *J*=13.8 Hz, Ar–CH_2–Ar *ax*), 3.77 (2H, t, *J*=8.3 Hz, 1× OCH_2), 3.07 (2H, d, *J*=14.4 Hz, Ar–CH_2–Ar *eq*), 2.72 (2H, d, *J*=13.8 Hz, Ar–CH_2–Ar *eq*), 1.95–1.79 (4H, m, 2× OCH_2CH_2), 0.95–0.84 (6H, m, 2× CH_3). ^{13}C NMR (75 MHz; CD_2Cl_2): δ 163.3, 157.2, 151.4, 144.4, 142.9, 141.6, 137.1, 135.8, 134.7, 132.8, 130.2, 129.7, 129.2, 128.5, 126.2, 124.8, 123.2, 77.5, 76.9, 32.0, 31.8, 23.4, 23.3, 9.8, 9.7. TOF MS (ES^+) *m*/*z* (%):$C_{46}H_{41}N_3O_{14}S_2$ (923.98) found: 946.3 (100) $[M+Na]^+$. EA calcd for $C_{46}H_{41}N_3O_{14}S_2$, C, 59.80; H, 4.47; N, 4.55; S, 6.94%. Found C, 59.72; H, 4.41; N, 4.51; S, 6.89%.

4.5. Synthesis of 5,17-dibromo-25,27-bis(*p*-nitrobenzenesulfonyloxy)-26,28-dipropoxycalix[4]arene (*cone*) 5

A mixture of calix[4]arene **2** (1.00 g, 1.14 mmol) and *N*-bromosuccinimide (NBS) (2.00 g, 11.3 mmol) in butan-2-one (50 ml) was stirred at room temperature for 7 days. The reaction mixture was then poured into 300 ml of 10% aqueous solution of Na_2SO_3 and extracted with dichloromethane (3×100 ml). The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure. The crude residue was dissolved in 10 ml of hot dichloromethane and precipitated by addition of methanol (150 ml). The precipitate was filtered off, washed with methanol and air dried to give 1.04 g (88%) of product **5** as grey powder, mp: 274–276 °C. ^1H NMR (300 MHz; $(CD_3)_2SO$): δ_H 8.51–8.48 (4H, m, Ar–H (Nos)), 8.09–8.06 (4H, m, Ar–H (Nos)), 7.44 (4H, s, Ar–H), 6.59 (2H, t, *J*=7.6 Hz, Ar–H), 6.35 (4H, d, *J*=7.6 Hz, Ar–H), 3.81 (4H, d, *J*=13.5 Hz, Ar–CH_2–Ar *ax*), 3.63 (4H, t, *J*=8.4 Hz, 2× OCH_2), 3.02 (4H, d, *J*=13.8 Hz, Ar–CH_2–Ar *eq*), 1.72–1.64 (4H, m, 2× OCH_2CH_2), 0.72 (6H, t, *J*=7.3 Hz, 2× CH_3). ^{13}C NMR (75 MHz; $(CD_3)_2SO$): δ 156.6, 151.9, 143.7, 140.4, 138.4, 134.1, 132.3, 130.7, 129.2, 126.6, 125.9, 115.6, 76.8, 31.0, 23.1, 10.1. TOF MS (ES^+) *m*/*z* (%): for $C_{46}H_{40}Br_2N_2O_{12}S_2$ (1036.77) found: 1061.5 (100) $[M+Na]^+$. EA calcd for $C_{46}H_{40}Br_2N_2O_{12}S_2$, C, 53.29; H, 3.89; N, 2.70; S, 6.19; Br, 15.41%. Found C, 53.05; H, 3.81; N, 2.51; S, 6.00; Br, 15.25%.

4.6. Synthesis of 5,17-diformyl-25,27-bis(*p*-nitrobenzenesulfonyloxy)-26,28-dipropoxycalix[4]arene (*cone*) 6

A mixture of calix[4]arene **2** (0.50 g, 0.57 mmol) and hexamethylenetetramine (2.87 g, 20.00 mmol) in trifluoroacetic acid (30 ml) was stirred at 80 °C under a nitrogen atmosphere for 22 h. After cooling to room temperature, the reaction mixture was carefully poured into 300 ml of cold water and extracted with CH_2Cl_2 (3×80 ml). The combined organic layers were washed with brine (200 ml) and dried over $MgSO_4$. The solvent was evaporated under reduced pressure, and the residue was dissolved in 10 ml of hot dichloromethane and precipitated by addition of methanol

(150 ml). The precipitate was filtered off, washed with methanol and air dried to give 400 mg (75%) of product **6** as a slightly brown powder, mp: 270 °C (decomp.). ^{1}H NMR (300 MHz; $(CD_3)_2SO$): δ_H 9.86 (2H, s, Ar–CHO), 8.52–8.49 (4H, m, Ar–H (Nos)), 8.14–8.11 (4H, m, Ar–H (Nos)), 7.80 (4H, s, Ar–H), 6.51 (2H, t, *J*=7.6 Hz, Ar–H), 6.29 (4H, d, *J*=7.6 Hz, Ar–H), 3.92 (4H, d, *J*=13.5 Hz, Ar–CH_2–Ar *ax*), 3.76 (4H, t, *J*=8.3 Hz, 2× OCH_2), 3.16 (4H, d, *J*=14.7 Hz, Ar–CH_2–Ar *eq*), 1.74–1.67 (4H, m, 2× OCH_2CH_2), 0.73 (6H, t, *J*=7.3 Hz, 2× CH_3). ^{13}C NMR (75 MHz; CD_2Cl_2): δ 191.2, 162.9, 151.4, 144.4, 141.5, 136.9, 133.6, 131.8, 131.2, 130.2, 128.9, 126.2, 124.8, 77.2, 31.9, 23.4, 9.8. TOF MS (ES$^+$) *m*/*z* (%): for $C_{48}H_{42}N_2O_{14}S_2$ (935.00) found: 957.6 (100) $[M+Na]^+$. EA calcd for $C_{48}H_{42}N_2O_{14}S_2$, C, 61.66; H, 4.53; N, 3.00; S, 6.86%. Found C, 61.52; H, 4.40; N, 2.89; S, 6.62%.

4.7. Deprotection of (*p*-nitrobenzenesulfonyl) group—general procedure

The corresponding calixarenes **4**–**6** were dissolved in a mixture of dichloromethane and ethanol (1:1, v/v) and 50 equiv of powdered potassium hydroxide was added. The reaction mixture was allowed to stir at room temperature for 24 h, then acidified with 1 M hydrochloric acid and extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried over $MgSO_4$, and the organic solvent was evaporated under reduced pressure.

4.7.1. Synthesis of 5,17-dinitro-26,28-dipropoxycalix[4]arene-25,27-diol (cone) **7**. General procedure was applied to 3.28 g of calixarene **3**, KOH (9.50 g) in 500 ml of ethanol, 500 ml of DCM and 3.5 ml of water.[13] The residue after evaporation was dissolved in 2 ml of dichloromethane and precipitated by addition of methanol (100 ml). The precipitate was filtered off to give 1.86 g (92%) of product **7** as an orange powder, mp: 224–227 °C. ^{1}H NMR (300 MHz; $CDCl_3$, Me_4Si): δ_H 7.96 (2H, s, Ar–OH), 7.85 (4H, s, Ar–H), 7.15 (4H, d, *J*=7.6 Hz, Ar–H), 6.74 (2H, t, *J*=7.6 Hz, Ar–H) 4.35 (4H, d, *J*=12.9 Hz, Ar–CH_2–Ar *ax*), 4.04 (4H, t, *J*=6.2 Hz, 2× OCH_2), 3.50 (4H, d, *J*=13.2 Hz, Ar–CH_2–Ar *eq*), 2.17–2.06 (4H, m, 2× OCH_2CH_2), 1.34 (6H, t, *J*=7.5 Hz, 2× CH_3). ^{13}C NMR (75 MHz; $CDCl_3$, Me_4Si): δ 157.4, 153.3, 145.0, 135.3, 129.4, 126.8, 124.9, 120.3, 79.4, 31.7, 23.7, 11.1. TOF MS (ES$^-$) *m*/*z* (%): for $C_{34}H_{34}N_2O_8$ (598.66) found: 619.2 (100) $[M+Na-2H]^-$. EA calcd for $C_{34}H_{34}N_2O_8$, C, 68.22; H, 5.72; N, 4.68%. Found C, 67.99; H, 5.60; N, 4.49%.

^{1}H NMR spectrum[12] (300 K, $CDCl_3$, Me_4Si) of isomer **7a** for comparison: δ_H (ppm): 9.44 (s, 2H, –OH), 8.05 (4H, s, Ar–H), 7.00 (4H, d, *J*=7.7 Hz, Ar–H), 6.85 (2H, t, *J*=7.7 Hz, Ar–H), 4.30 (4H, d, *J*=13.2 Hz, Ar–CH_2–Ar *ax*), 4.02 (4H, t, *J*=6.0 Hz, –O–CH_2CH_2), 3.51 (4H, d, *J*=13.2 Hz, Ar–CH_2–Ar *eq*), 2.27–2.03 (4H, m, –OCH_2CH_2–), 1.33 (6H, t, *J*=7.1 Hz, –CH_3).

4.7.2. Synthesis of 5-mononitro-26,28-dipropoxycalix[4]arene-25,27-diol (cone) **8**. General procedure was applied to 663 mg of calixarene **4**, KOH (2.00 g) in 100 ml of ethanol and 100 ml of dichloromethane. The residue after evaporation was dissolved in 1 ml of dichloromethane and precipitated by addition of methanol (50 ml), and the precipitate was filtered off to give 231 mg (58%) of product **8** as yellow powder, mp: 223–226 °C. ^{1}H NMR (300 MHz; $CDCl_3$, Me_4Si): δ_H 8.05 (2H, s, Ar–H), 7.80 (2H, s, Ar–OH), 7.12–7.08 (4H, m, Ar–H), 6.92 (2H, d, *J*=7.6 Hz, Ar–H), 6.74 (1H, t, *J*=7.5 Hz, Ar–H), 6.70 (2H, t, *J*=7.5 Hz, Ar–H) 4.39 (2H, d, *J*=13.2 Hz, Ar–CH_2–Ar *ax*), 4.28 (2H, d, *J*=12.9 Hz, Ar–CH_2–Ar *ax*), 4.03 (2H, t, *J*=6.3 Hz, 1× OCH_2), 4.00 (2H, t, *J*=6.3 Hz, 1× OCH_2), 3.46 (2H, d, *J*=14.1 Hz, Ar–CH_2–Ar *eq*), 3.41 (2H, d, *J*=13.5 Hz, Ar–CH_2–Ar *eq*), 2.16–2.02 (4H, m, 2× OCH_2CH_2), 1.33 (3H, t, *J*=7.5 Hz, 1× CH_3), 1.32 (3H, t, *J*=7.5 Hz, 1× CH_3). ^{13}C NMR (75 MHz; $CDCl_3$, Me_4Si): δ 157.9, 153.5, 151.9, 144.8, 135.4, 133.4, 129.3, 128.3, 128.2, 126.9, 125.8, 124.9, 119.8, 79.2, 78.7, 31.7, 31.6, 23.7, 11.2, 11.1. TOF MS (ES$^-$) *m*/*z* (%): for $C_{34}H_{35}NO_6$ (553.66) found: 574.2 (100) $[M+Na-2H]^-$. EA calcd for $C_{34}H_{35}NO_6$, C, 73.76; H, 6.37; N, 2.53%. Found C, 73.42; H, 6.31; N, 2.39%.

4.7.3. Synthesis of 5,17-dibromo-26,28-dipropoxycalix[4]arene-25,27-diol (cone) **9**. General procedure was applied to 100 mg of calixarene **6**, KOH (270 mg) in 20 ml of ethanol and 20 ml of dichloromethane. No further purification was needed, and product **9** was obtained in 97% yield (62 mg) as a white powder, mp: 214–216 °C. ^{1}H NMR (300 MHz; $CDCl_3$, Me_4Si): δ_H 8.22 (2H, s, Ar–OH), 7.08 (4H, s, Ar–H), 7.04 (4H, d, *J*=7.3 Hz, Ar–H), 6.66 (2H, t, *J*=7.5 Hz, Ar–H) 4.26 (4H, d, *J*=12.9 Hz, Ar–CH_2–Ar *ax*), 3.95 (4H, t, *J*=6.2 Hz, 2× OCH_2), 3.35 (4H, d, *J*=13.2 Hz, Ar–CH_2–Ar *eq*), 2.11–2.00 (4H, m, 2× OCH_2CH_2), 1.31 (6H, t, *J*=7.5 Hz, 2× CH_3). ^{13}C NMR (75 MHz; $CDCl_3$, Me_4Si): δ 153.5, 151.4, 135.9, 132.2, 129.0, 127.4, 119.7, 117.9, 78.8, 31.6, 23.7, 11.1. TOF MS (ES$^-$) *m*/*z* (%): for $C_{34}H_{34}Br_2O_4$ (666.46) found. 665.2 (100) $[M-H]^-$. EA calcd for $C_{34}H_{34}Br_2O_4$, C, 61.28; H, 5.14; Br, 23.98%. Found C, 61.02; H, 5.02; Br, 23.73%.

4.7.4. Synthesis of 5,17-diamino-26,28-dipropoxycalix[4]arene-25,27-diol (cone) ***10***. A catalytic amount (10 mg) of Raney nickel was added to the solution of calix[4]arene **7** (400 mg, 0.67 mmol) and hydrazine monohydrate (1.5 ml) in methanol (100 ml), and resulting mixture was heated to reflux. After 7 h the same amount of hydrazine monohydrate (1.5 ml) and Raney nickel was added once again and the mixture was refluxed for further 15 h. After cooling to room temperature, the resulting suspension was filtered through the short column of Celite, the column was washed by additional 50 ml of MeOH, and the solvent was removed under reduced pressure. The solid residue was dissolved in 100 ml of CH_2Cl_2, washed with water, brine and dried over $MgSO_4$. The evaporation of solvent gave 262 mg of product **10** (73%) as a brown powder, mp: 313–315 °C. ^{1}H NMR (300 MHz; $CDCl_3$, Me_4Si): δ_H 8.43 (2H, s, Ar–OH), 7.01 (4H, d, *J*=7.3 Hz, Ar–H), 6.63 (2H, t, *J*=7.3 Hz, Ar–H), 6.22 (4H, s, Ar–H), 4.24 (4H, d, *J*=12.6 Hz, Ar–CH_2–Ar *ax*), 3.91 (4H, t, *J*=6.3 Hz, 2× OCH_2), 3.24 (4H, d, *J*=12.9 Hz, Ar–CH_2–Ar *eq*), 3.16 (4H, br s, Ar–NH_2), 2.07–1.96 (4H, m, 2× OCH_2CH_2), 1.29 (6H, t, *J*=7.5 Hz, 2× CH_3). ^{13}C NMR (75 MHz; $CDCl_3$, Me_4Si): δ 153.8, 145.0, 143.1, 134.2, 128.6, 128.4, 118.9, 116.2, 78.5, 31.8, 23.7, 11.2. MS ESI$^-$ *m*/*z* (%): for $C_{34}H_{38}N_2O_4$ (538.30) found: 537.2 (100) $[M-H]^-$. EA calcd for $C_{34}H_{38}N_2O_4$, C, 75.86; H, 7.12; N, 5.20%. Found C, 75.53; H, 7.10; N, 5.13%.

4.7.5. Synthesis of 5,17-bis(N′-phenylureido)-26,28-dipropoxycalix[4]arene-25,27-diol (cone) ***11***. Phenyl isocyanate (110 mg, 0.92 mmol) was added to a solution of calix[4]arene **10** (100 mg, 0.18 mmol) in 30 ml of dry CH_2Cl_2 under nitrogen atmosphere. The mixture was stirred for 3 days at room temperature. Then, 10 ml of MeOH was added to quench the reaction, and solution was stirred for further 2 h. Solvents were removed under reduced pressure and the residue was purified by column chromatography (Al_2O_3, eluent CH_2Cl_2/MeOH=100:1) to give 115 mg of product **11** (79%), R_f=0.7, as a slightly brown solid, mp: 224–226 °C. ^{1}H NMR (300 MHz; DMSO-d_6): δ_H 8.55 (2H, s, Ar–OH), 8.43 (2H, s, NH), 8.29 (2H, s, NH), 7.33 (4H, d, *J*=9.7 Hz, Ar–H), 7.19 (4H, t, *J*=8.1 Hz, Ar–H), 7.11–7.09 (8H, m, Ar–H), 6.89 (2H, t, *J*=7.3 Hz, Ar–H), 6.57 (2H, t, *J*=7.5 Hz, Ar–H), 4.15 (4H, d, *J*=12.9 Hz, Ar–CH_2–Ar *ax*), 3.91 (4H, t, *J*=5.71 Hz, 2× OCH_2), 3.40 (4H, d, *J*=12.9 Hz, Ar–CH_2–Ar *eq*), 2.02–1.91 (4H, m, 2× OCH_2CH_2), 1.30 (6H, t, *J*=7.3 Hz, 2× CH_3). ^{13}C NMR (75 MHz; $CDCl_3$:DMSO-d_6 4:1, v/v): δ 152.2, 151.8, 146.0, 138.5, 135.0, 321.8, 127.6, 127.4, 126.8, 120.8, 118.4, 117.9, 117.3, 77.2, 30.2, 22.2, 9.8. MS ESI$^+$ *m*/*z* (%): for $C_{48}H_{48}N_4O_6$ (776.94) found: 815.4 (100) $[M+K]^+$, 799.8 (80) $[M+Na]^+$, 777.26 (100) $[M]^+$. EA calcd for $C_{48}H_{48}N_4O_6$, C, 74.21; H, 6.23; N, 7.21%. Found C, 74.10; H, 6.15; N, 7.20%.

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